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## **Is preeclampsia associated with restless legs syndrome?**

Ramirez, J O ; Cabrera, S A S ; Hidalgo, H ; Cabrera, S G ; Linnebank, M ; Bassetti, C L ; Kallweit, U

**Abstract:** **OBJECTIVE:** Restless legs syndrome (RLS) is a common neurologic disorder. Secondary RLS includes pregnancy and iron deficiency. Prevalence of RLS in pregnancy ranges from 11% to 27%. We aimed to assess the frequency and characteristics of RLS in pregnancy in a Peruvian population and to evaluate the possible pregnancy or delivery complications due to RLS. **METHODS:** We assessed 218 consecutive expectant mothers at the inpatient clinic of the Hospital San Bartolome in Lima, Peru. Assessment was performed by using the standard diagnostic criteria for RLS and by using a clinical and diagnostic interview. Questionnaires for RLS severity, idiopathic RLS (IRLS), and excessive daytime sleepiness (EDS) according to the Epworth sleepiness scale (ESS) were used. Blood examination was performed for hemoglobin and hematocrit. For comparison, RLS patients were matched for age and body mass index (BMI) with pregnant women without RLS. **RESULTS:** Out of 218 patients, 40 (18.4%) fulfilled diagnostic criteria for RLS. In RLS patients, prophylactic iron supplementation therapy during pregnancy was less frequently taken ( $P=.02$ ). Pregnant women with RLS had a higher ESS score than pregnant controls ( $10.6 \pm 3.1$  vs  $7.6 \pm 3.6$ ;  $P<.001$ ). Preeclampsia was more frequent in RLS ( $7/40$  vs  $1/39$ ;  $P=.03$ ). **CONCLUSIONS:** In our study, RLS was frequent in pregnant Peruvian women, especially in those without prophylactic iron supplementation. RLS patients described more EDS. Preeclampsia was more common in RLS. Our study is the first study to indicate a possible association between RLS and preeclampsia.

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# **Is Preeclampsia Associated with Restless Legs Syndrome?**

J.O. Ramirez (1), S.A.S. Cabrera (1), H. Hidalgo (2), S.G. Cabrera (1), M. Linnebank (3),  
C.L. Bassetti (3), U. Kallweit\* (2,3)

1) Hospital Nacional Docente Madre Niño San Bartolome, Lima, Peru

2) Department of Neurology, Neuropsychiatry and Sleep Medicine, Fachklinik

Katzenelnbogen, Germany

3) Department of Neurology, University Hospital Zurich, Switzerland

## \*Corresponding Author:

Ulf Kallweit, MD  
Department of Neurology  
University Hospital Zurich  
Frauenklinikstrasse 26  
8091 Zürich  
Switzerland  
Tel. +41 44 255 1111  
Fax. +41 44 255 4380  
Email: ulf.kallweit@usz.ch

## Key words:

Restless legs syndrome; preeclampsia; pregnancy; iron deficiency; excessive daytime  
sleepiness; Epworth sleepiness scale

## **Abstract**

### **Objective:**

Restless legs syndrome (RLS) is a common neurological disorder. Secondary RLS includes pregnancy and iron deficiency. Prevalence of RLS in pregnancy ranges between 11-27%. We aimed at assessing frequency and characteristics of RLS in pregnancy in a Peruvian population and to evaluate possible pregnancy or delivery complications due to RLS.

### **Methods:**

We assessed 218 consecutive expectant mothers at the inpatient clinic of the Hospital San Bartolome, Lima, Peru. Assessment was performed by using the standard diagnostic criteria for RLS and by a clinical-diagnostic interview. Questionnaires for RLS severity (IRLS) and excessive daytime sleepiness (EDS) by Epworth Sleepiness Scale (ESS) were used. Blood examination was performed for hemoglobin and hematocrit. For comparison, RLS patients were matched for age- and BMI with pregnant women without RLS.

### **Results:**

Out of 218 patients, 40 (18.4%) fulfilled diagnostic criteria for RLS. In RLS patients, prophylactic iron supplementation therapy during pregnancy was taken less frequently ( $p=0.02$ ). Pregnant women with RLS had a higher ESS score than pregnant controls ( $10.6 \pm 3.1$  vs.  $7.6 \pm 3.6$ ;  $p<0.001$ ). Preeclampsia was more frequent in RLS ( $7/40$  vs.  $1/39$ ;  $p=0.03$ ).

### **Conclusions:**

In our study, RLS was frequent in pregnant Peruvian women, especially in those without prophylactic iron supplementation. RLS patients described more daytime sleepiness. Preeclampsia was more common in RLS. This is the first study indicating a possible association between RLS and preeclampsia.

## Introduction

Restless Legs Syndrome (RLS), is one of the most common movement and sleep disorders with a frequency of 2 to 10% in the general population.<sup>1</sup> Diagnostic criteria<sup>2</sup> include an urge to move, usually focused on the legs, which begins or worsens during periods of rest or inactivity. Further, symptoms improve by movement and have strong circadian presentation with a worsening in the evening and night. RLS is usually associated with insomnia and sometimes with excessive daytime sleepiness.<sup>3,4</sup> Associations with psychiatric disorders (anxiety, depression) and cardiovascular disorders (hypertension, coronary artery disease) are postulated.<sup>5,6</sup>

The pathogenesis of RLS remains unclear, but most probably, a brain iron deficiency produces a dopaminergic pathology producing the RLS symptoms.<sup>7,8</sup>

RLS is categorized as either primary (idiopathic) or secondary depending on clinical features. Secondary (symptomatic) RLS can occur due to (e.g.) iron deficiency, folate deficiency or pregnancy. In European and North American countries, a prevalence of 11-27%, in Brazil 13.5% or Pakistan 30% of RLS in pregnancy has been described.<sup>9-11</sup> In pregnancy, the majority experience RLS for the first time or experience a worsening of symptoms.<sup>9</sup> RLS often occurs during the 3rd trimester. The appearance of RLS in pregnancy is a risk factor for a later occurring, often chronic RLS. Symptoms are usually transient: In 2/3 of patients, RLS disappears within 2 weeks after delivery.<sup>9,12</sup>

There are different hypotheses for the occurrence of RLS in pregnancy. Under hypothesis: 1. hormonal. An increase of prolactin and/or estrogen alters dopamine metabolism. 2. psychomotor behaviour hypothesis: pregnancy is a period of reduced activity. 3. metabolic hypothesis: iron and/or folate deficiency in pregnancy is frequent.<sup>9,13,14</sup>

The treatment of RLS includes iron supplementation, dopaminergic agents, opioids, and antiepileptic drugs. Dopaminergic medications are currently considered the treatment of

choice for RLS.<sup>5,6</sup> In pregnancy, oral (or intravenous) iron supplementation is recommended.

<sup>15</sup> For oral supplementation there is no evidence for any benefit on RLS.

Preeclampsia is a severe complication of pregnancy and includes the symptoms: hypertension (>140/90 mmHg), proteinuria (>300mg/ 24h), and edema (especially hands and face) and has a prevalence of 6-8% worldwide. For a diagnosis, only hypertension (two separate readings taken at least six hours apart of 140 or more in systolic blood pressure and/or 90 or more in diastolic blood pressure) and proteinuria (300 mg of protein in a 24-hour urine sample) are necessary. In Peru, preeclampsia occurs in 10% of pregnancies.<sup>16</sup> The incidence of preeclampsia at the Hospital Nacional San Bartolome is 7%.<sup>17</sup> Pathogenesis of preeclampsia is still poorly understood and includes genetic, anatomic, nutritional, vascular, inflammatory, metabolic, social and emotional factors.<sup>18-20</sup> Preeclampsia and eclampsia are maternal and fetal syndromes, probably secondary due to imperfect placentation, inadequate blood perfusion, hypoxia and excessive placental production of soluble fms-like tyrosine kinase-1 (sFlt-1).<sup>21</sup> sFlt-1 is a potent angiogenic growth factor, antagonizes vascular endothelial growth factor (VEGF) and PlGF (placental growth factor), and leads to a damaged maternal endothelium and restriction of placental growth. Consequently maternal hypertension and proteinuria occur.<sup>19-21</sup>

Possible risk factors include pre-existing hypertension, diabetes, autoimmune diseases such as lupus, and a family history of preeclampsia. When preeclampsia occurs, it often comes to abortion or an induced delivery, partially by caesarian section. In Peru, preeclampsia is the principal cause of morbidity and mortality in pregnant women and their fetus<sup>22,23</sup> and also the cause second frequently for maternal mortality.<sup>24</sup>

Pregnancy or delivery complications due to RLS are not described.

*Objective:* To assess the frequency and characteristics of RLS in pregnancy in a Peruvian population with a particular focus on pregnancy and delivery complications.

## **Patients and Methods**

This study was conducted at the *Hospital Nacional Docente Madre Niño San Bartolome, Lima, Peru* from June 1<sup>st</sup>, 2011 until June 30<sup>th</sup>, 2011.

*Ethics:* The study protocol was approved by the local Institutional Review Boards, and all patients gave written informed consent. The study was performed according the principles of the Helsinki Declaration of 1975.

*Subjects and clinical assessment:* During the above-mentioned period, 218 consecutive expectant mothers were admitted for delivery. Assessment included a clinical-diagnostic face-to-face interview by a trained and experienced neurologist for RLS symptoms and was performed during the peripartum period (+/- 1 day), usually the day after delivery. The diagnosis of RLS was made according to standard criteria.<sup>2</sup> Other RLS associated conditions were excluded. We compared RLS patients with age- and BMI- matched controls (expectant mothers). Iron supplementation was defined as “daily or almost daily (at least 5 times per week) oral intake of iron supplementation (any dosage)”. Preeclampsia was diagnosed according international criteria.<sup>25</sup>

*Questionnaires and laboratory examination:* The IRLSSG score is a commonly used tool to measure to severity of the disease.<sup>2</sup> Sleepiness was assessed using the Epworth Sleepiness Scale (ESS), with scores  $\geq 10$  indicating excessive daytime sleepiness (EDS).<sup>26</sup> For IRLSSG and ESS we used validated Spanish versions.<sup>2,27</sup> Laboratory examination included hemoglobin and hematocrit.

*Statistics.* Continuous data are expressed as means and standard deviation (SD), categorical variables as numbers and percentage. All analyses were performed with the Statistical Package for the Social Sciences (SPSS, version 17.0). For univariate analysis we used Student's *t*-test (for numerical scale variables) and  $\chi^2$ -test (for nominal scale variables). Correlation analyses were performed using the Pearson coefficient. Significance was accepted at  $p < 0.05$ .

## Results

### *Patients and RLS characteristics*

Mean age of all 218 expectant mothers was 26.7 years (SD  $\pm$  6.3, range 15-45) and mean BMI was 24.8 ( $\pm$ 4.8). Out of 218 patients, 40 (18.4%) fulfilled diagnostic criteria for RLS. Mean IRLSSG score was 16.6 ( $\pm$  6.3), frequency of symptoms was 4.3 ( $\pm$  2.5) days/ week and 10/40 (25%) described RLS in previous pregnancies.

### *Demographic, clinical characteristics and pregnancy / delivery complications in expectant mothers with and without RLS*

Expectant women with RLS (n=40) were matched for pregnant women without RLS (n=39). Between groups, there were no differences in age, actual BMI, BMI before pregnancy, hemoglobin, hematocrit or pregnancy/ delivery adverse events in general. Pregnant women had higher scores on ESS ( $p < 0.01$ ) than expectant women without RLS, took prophylactic daily iron supplementation ( $p = 0.02$ ) less frequently and suffered more often from preeclampsia ( $p = 0.03$ ).

For further details please see *table 1*.

## Discussion

RLS is a frequent, but often underestimated and underdiagnosed neurological disorder. In pregnancy, RLS often occurs in the 3rd trimester. Our results with a frequency of 18.4% of RLS in pregnancy are in line with published data on the prevalence of RLS in pregnancy (11-30%).

In a proportion of RLS patients (20-30%), excessive daytime sleepiness (EDS, as measured by ESS) occurs. Limited data indicate no particular demographic or clinical differences between “sleepy” and “non-sleepy” RLS patients. In our study, expecting mothers with RLS suffered more frequently from EDS. Clinically and laboratory (hemoglobin and hematocrit) analysis revealed similar findings between groups. Thus EDS is unlikely attributed to clinical

or laboratory differences but to RLS. Other reasons for these differences include poor sleep or sleep deprivation.

Iron supplementation was infrequent in pregnant women with RLS, possibly indicating consecutive lower iron levels that may have contributed to RLS. In a recent study by Siddiqui et al.<sup>28</sup>, mean serum ferritin concentration in preeclamptics was higher than in normal pregnant women. In this study, no significant differences were found among hemoglobin concentration or hematocrit, either.

This is the first study indicating a possible association between the occurrence of RLS in pregnancy and preeclampsia. Significantly more women with RLS suffered from preeclampsia compared to women without RLS (17.5% vs. 3%,  $p=0.03$ ). Pathogenesis of preeclampsia still remains unclear. Different hypotheses for the occurrence of preeclampsia due to RLS include changes in iron status or disturbances in the blood pressure regulation by an elevated sympathetic activation, as RLS is associated with hypertension.

#### *Limitations:*

We have to acknowledge several limitations. We could not include laboratory measurements of iron status - ferritine. Thus relationship between iron deficiency in pregnancy and RLS remains mainly theoretical. Diagnosis of preeclampsia was made according diagnostic criteria. Detailed data on blood pressure levels and other symptoms of preeclampsia are lacking. During pregnancy, no patient has been treated for RLS and usually any treatment is reduced to a minimum. Nevertheless we had no data on medication of expecting mothers. Further, mean ESS scores were different between groups but did not reach cut off score for a pathologic degree of daytime sleepiness.

In conclusion, pregnant women should be screened for RLS and EDS, as both are frequent complications of pregnancy. The role of RLS, iron and folate deficiency for the incidence of preeclampsia should be analyzed in larger studies.



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**Legends:**

**Table 1**

Demographic, clinical characteristics and pregnancy / delivery complications in expectant mothers with and without RLS (matched controls)

**Table 1**

	RLS	Controls	<i>p</i>
N	40	39	
Age [y]	27.2 ± 6.7	25.9 ± 5.6	n.s.
BMI (actual)	30.5 ± 4.5	29.4 ± 6.8	n.s.
BMI (before pregnancy)	24.7 ± 4	24.8 ± 5.6	n.s.
IRLS	16.6 (± 6.3)		
ESS	10.6 ± 3.9	7.6 ± 3.1	<0.01
Daily iron supplementation (n)	13/40 (32.5%)	18/39 (46.2%)	0.02
Hemoglobin (g/dl)	9.8 ± 2.3	10.5 ± 1.5	n.s.
Hematocrit (%)	32.5 ± 4	32.2 ± 4.6	n.s.
Pregnancy or delivery			
associated adverse events (n)	9	3	n.s.
-Preeclampsia (n)	7 (17.5%)	1 (3%)	0.03
-Post-partum haemorrhage (n)	2	1	n.s.
-Other (n)	0	1	n.s.

BMI: Body-Mass-Index [kg/m<sup>2</sup>]

ESS: Epworth Sleepiness Scale